

Synthesis of Methyl-substituted Lariat Ethers Containing a 13-Crown-4 Ring

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Convenient synthetic procedures for preparing two kinds of methyl-substituted lariat ethers containing a 13-crown-4 ring, **1** and **2**, are described. Compounds **1a-c** were obtained from the reaction of 2-bromo-2-methyl-2-methyl-13-crown-4 (**5**) with the appropriate alkoxide. Compound **5** was prepared without the need for prior protection of the bromomethyl group. For the synthesis of compounds **2a-c**, which possess an electron-donating group on the central carbon of the trimethyl moiety of the 13-crown-4 ring, the substituents were introduced before cyclization.

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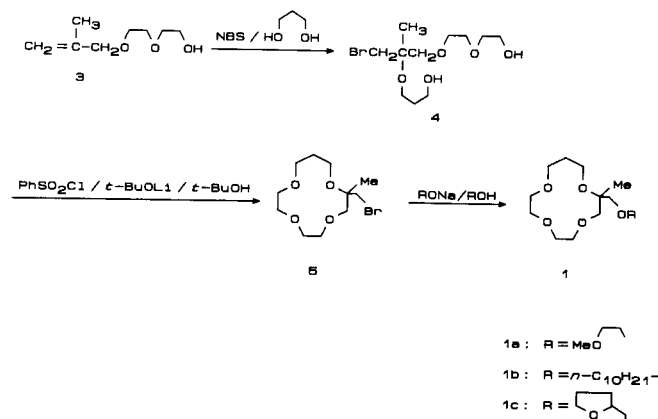
Introduction.

Crown ethers are interesting compounds because they selectively complex not only with a variety of inorganic and organic cations but also with neutral molecules [1]. Crown ethers which possess only oxygen hetero-atoms show excellent complexation properties toward hard cations such as alkali and alkaline earth metal cations [2].

Recently, we found that crown ether derivatives which contain an electron-donating side arm and a methyl group on the same carbon atom ("methyl-substituted lariat ethers") were excellent complexing agents for alkali metal cations based on the effective coordination of the side arm [3-5]. The 15-crown-5 and 18-crown-6 derivatives show such selectivity toward Na⁺ and K⁺, respectively. On the other hand, the development of new ligands for lithium ions is highly desired [6]. Previous studies strongly suggest that a 13- or 14-crown-4 ring is suitable for complexation with Li⁺ [7-12].

From this point of view, we attempted the synthesis of two kinds of methyl-substituted lariat ethers containing a 13-crown-4 ring.

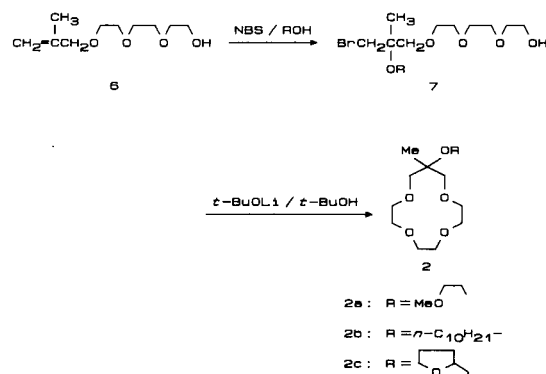
Scheme 1



Results and Discussion.

The synthetic procedures are summarized in Schemes 1

Scheme 2



and 2. Intermolecular bromoalkoxylation of diethylene glycol 2-methylallyl ether (**3**) with *N*-bromosuccinimide (NBS) in an excess of 1,3-dihydroxypropane gave the corresponding diol **4** in a 48% yield. The removal of the succinimide formed during the course of reaction is the key step in the success of the following cyclization, because its presence resulted in the formation of a remarkable amount of unknown by-products in the cyclization step. The presence of succinimide in crude **4** was checked by the absorption at 1700 cm⁻¹ (ν C=O) with ir spectroscopy.

A mixture of **4** and benzenesulfonyl chloride in *t*-butyl alcohol was added dropwise to a *t*-butyl alcohol solution containing lithium *t*-butoxide as the base over a period of 4 hours at 40° to give 2-bromo-2-methyl-13-crown-4 (**5**) in a 33% yield according to a high-dilution intramolecular cyclization method, which we reported previously [13]. Although the template effect by the lithium ion was not as pronounced in comparison with the synthesis of 15-crown-5 or 18-crown-6 ethers, a new 13-crown-4 ether with a reactive bromomethyl group was obtained without the need for protection of the bromo group.

Derivatization to lariat ethers was performed according to the conventional method [3]. Compound **1** was obtained by the reaction of **5** with the sodium alkoxide of the corresponding alcohol at 120° for 24 hours.

Several 12-substituted lariat ethers based on the 13-crown-4 ether **2** were prepared according to Scheme 2. The electron-donating substituent was introduced prior to cyclization using the conventional bromoalkoxylation reaction.

The study of the complexation properties of **1** and **2** for alkali metal cations is now in progress.

EXPERIMENTAL

The proton nmr spectra were taken at 400 MHz on a JEOL JNM-ASX-400 spectrometer, using tetramethylsilane as the internal standard. Infrared (ir) spectra were obtained on a Hitachi 260-10 spectrometer. The mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV. Diethylene glycol mono-2-methylallyl ether (**3**) and triethylene glycol mono-2-methylallyl ether (**6**) were prepared according to the literature [3].

2-Bromomethyl-2-methyl-1,4,7,10-tetraoxacyclotridecane (**5**).

To a stirred suspension of *N*-bromosuccinimide (NBS) (17.8 g, 0.1 mole) in propylene glycol (38.0 g, 0.5 mole) was added **3** (16.0 g, 0.1 mole) over a period of 1 hour at 40°. The mixture was stirred at 50° for another 5 hours. After cooling to room temperature, the insoluble material (succinimide) was removed by filtration. Excess alcohol and the residual succinimide were removed under reduced pressure (150°/0.01 mm) to give a brown viscous oil (15.1 g, 48%). This compound **4** was used for the next step without further purification. To a stirred solution of lithium (0.89 g, 0.12 mole) in *t*-butyl alcohol (200 ml) was added a mixture of **4** (5.1 g, 0.016 mole) and benzenesulfonyl chloride (3.18 g, 0.018 mole) in *t*-butyl alcohol (100 ml) over a period of 5 hours at 40°. After all insoluble matter was removed by filtration and washed with dichloromethane, the solvent was evaporated. Water (100 ml) was added to the residue and extracted with dichloromethane (200 ml). After evaporation, the residue was distilled in a Kugelrohr apparatus (90°/0.01 mm) to give a slightly yellow oil (1.57 g, 33%); ir (neat): 2900, 2850, 1450, 1360, 1250, 1130, 920 cm⁻¹; ms: (m/e) 298 (M⁺+2), 296 (M⁺), 217 (9), 203 (6), 115 (30), 103 (31), 87 (25), 45 (100); ¹H nmr (deuteriochloroform): δ 1.26 (s, 3H), 1.72-1.90 (m, 2H), 3.44-3.76 (m, 16H).

Anal. Calcd. for C₁₁H₂₁O₄Br: C, 44.46; H, 7.12; Br, 26.89. Found: C, 44.60; H, 7.09; Br, 27.11.

General Procedure for the Synthesis of Lariat Ethers.

A simple substitution reaction of the bromomethyl methyl crown ether with an appropriate sodium alkoxide was used for the synthesis. After sodium metal (0.2 g, 9 mmoles) was dissolved in the alcohol (60 mmoles), the bromomethyl methyl crown ether (3 mmoles) was added to the mixture. The mixture was stirred at 120° for 24 hours. For solid alcohols, diglyme (20 ml) was used to dissolve the compound. After the mixture was cooled to room temperature, dichloromethane (20-50 ml) was added to the residue and the insoluble matter was removed by filtration. The resulting mixture was then concentrated and distilled in a Kugelrohr apparatus under reduced pressure (150-200°/0.01 mm) to pyrolyze the complex. The volatile components were redistilled using the Kugelrohr apparatus.

2-[(2-Methoxyethoxy)methyl]-2-methyl-1,4,7,10-tetraoxacyclotridecane (**1a**).

The yield of **1a** was 72%, bp 80°/0.02 mm (Kugelrohr); ir (neat): 2920, 2860, 1450, 1370, 1250, 1110 cm⁻¹; ms: (m/e) 292 (M⁺, 9), 203 (11), 115 (100), 101 (26), 59 (90); ¹H nmr (deuteriochloroform): δ 1.18 (s, 3H), 1.60-1.94 (m, 2H), 3.32 (s, 3H), 3.42-3.86 (m, 20H).

Anal. Calcd. for C₁₄H₂₈O₆: C, 57.51; H, 9.65. Found: C, 57.40; H, 9.73.

2-[(Decyloxy)methyl]-2-methyl-1,4,7,10-tetraoxacyclotridecane (**1b**).

The yield of **1b** was 40%, bp 100°/0.01 mm (Kugelrohr); ir (neat): 2930, 2860, 1460, 1360, 1250, 1100 cm⁻¹; ms: (m/e) 374 (M⁺, 6), 203 (15), 145 (20), 101 (45), 45 (100); ¹H nmr (deuteriochloroform): δ 0.74-1.08 (t, 3H), 1.18 (s, 3H), 1.26-1.54 (m, 16H), 1.62-1.90 (m, 2H), 3.48-3.98 (m, 18H).

Anal. Calcd. for C₂₁H₄₂O₅: C, 67.34; H, 11.30. Found: C, 67.02; H, 11.44.

2-Methyl-2-[(2-tetrahydrofuranyl)methyl]oxy]methyl]-1,4,7,10-tetraoxacyclotridecane (**1c**).

The yield of **1c** was 57%, bp 85°/0.01 mm (Kugelrohr); ir (neat): 2880, 1480, 1360, 1250, 1110, 930 cm⁻¹; ms: (m/e) 318 (M⁺, 14), 203 (15), 115 (42), 101 (36), 59 (52), 45 (100); ¹H nmr (deuteriochloroform): δ 1.18 (s, 3H), 1.62-2.00 (m, 6H), 3.42-3.92 (m, 21H).

Anal. Calcd. for C₁₆H₃₀O₆: C, 60.36; H, 9.50. Found: C, 60.61; H, 9.88.

12-[(2-Methoxyethoxy)methyl]-12-methyl-1,4,7,10-tetraoxacyclotridecane (**2a**).

The bromoalkoxylation of **6** using NBS in ethylene glycol monomethyl ether was carried out as previously mentioned. The crude bromoalkoxylated intermediate **7** was refluxed for 30 hours in *t*-butyl alcohol containing lithium *t*-butoxide. The yield was calculated based on the starting **6** (10%). bp 110°/0.01 mm (Kugelrohr); ir (neat): 2930, 2870, 1430, 1260, 1120, 910 cm⁻¹; ms: (m/e) 278 (M⁺, 14), 202 (4), 147 (10), 103 (13), 101 (15), 87 (11), 59 (100), 45 (38); ¹H nmr (deuteriochloroform): δ 1.16 (s, 3H), 3.38 (s, 3H), 3.52-3.82 (m, 20H).

Anal. Calcd. for C₁₃H₂₆O₆: C, 56.10; H, 9.42. Found: C, 55.92; H, 9.40.

12-[(Decyloxy)methyl]-12-methyl-1,4,7,10-tetraoxacyclotridecane (**2b**).

The overall yield for **2b** was 15%, bp 110°/0.02 mm (Kugelrohr); ir (neat): 2920, 2880, 1420, 1250, 1110, 920 cm⁻¹; ms: (m/e) 360 (M⁺, 9), 202 (5), 103 (16), 101 (22), 87 (10), 59 (100), 45 (36); ¹H nmr (deuteriochloroform): δ 0.76-1.10 (t, 3H), 1.16 (s, 3H), 1.24-1.58 (m, 16H), 3.48-3.78 (m, 18H).

Anal. Calcd. for C₂₀H₄₀O₅: C, 66.63; H, 11.18. Found: C, 66.88; H, 11.02.

12-Methyl-12-[(2-tetrahydrofuranyl)methyl]oxy]methyl]-1,4,7,10-tetraoxacyclotridecane (**2c**).

The overall yield was 14%, bp 100°/0.01 mm (Kugelrohr); ir (neat): 2880, 1460, 1360, 1110, 930 cm⁻¹; ms: (m/e) 304 (M⁺, 21), 202 (4), 103 (65), 101 (19), 89 (16), 59 (100), 45 (38); ¹H nmr (deuteriochloroform): δ 1.20 (s, 3H), 1.58-1.98 (m, 4H), 3.40-3.88 (m, 21H).

Anal. Calcd. for C₁₅H₂₈O₆: C, 59.19; H, 9.27. Found: C, 58.94; H, 9.06.

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